Double Oscillating Diffusion Encoding (DODE) augments microscopic anisotropy contrast

Noam Shemesh[1], Andrada Ianuş[2], Daniel C Alexander[2], and Ivana Drobnjak[2]

[1]*Champalimaud Neuroscience Programme, Champalimaud Center for the Unknown, Lisbon, Portugal,* [2]*Center for Medical Image Computing, Department of Computer Science, University College London, London, United Kingdom*

Target audience. Researchers and clinicians interested in the brain's microarchitecture and diffusion MR methods.

Purpose. Generating a methodology capable of amplifying Double-Diffusion-Encoding MR's sensitivity towards randomly oriented compartments.

Introduction. Double Diffusion Encoding (DDE, Fig. 1A) [1] NMR and MRI techniques – more commonly known as Double Wave Vector (DWV) [2] or double-Pulsed-Field-Gradient (dPFG) [3,4] – can resolve underlying microstructures of highly heterogeneous systems [3,4], which are prevalent in, e.g., Gray Matter (GM) tissues [2,3]. Angular DDE (Fig. 1B) provides its microstructural contrast in a model-free fashion by varying the relative orientation between $\mathbf{G_1}$ and $\mathbf{G_2}$ at long mixing time (t_m), or, alternatively, by selecting wavevector schemes that deliver rotationally invariant metrics on the underlying compartment eccentricity [5,6]. At the heart of DDE experiments lies an amplitude modulation which represents the system's microscopic anisotropy (μA). If the system is *a-priori* randomly oriented, DDE's contrast can be quantified from the ratiometric signals at ψ=0° and ψ=90° [3,4]; a similar concept holds true for rotationally-invariant DDE schemes [5,6].

Here, we present a novel class of sequences, termed Double-Oscillating-Diffusion-Encoding (DODE, Fig. 1C), which consist of two successive oscillating gradient encodings. Just as Oscillating-Gradient Spin-Echo (OGSE) modifications could augment size sensitivity in Single-Diffusion-Encoding (SDE) MR [7], we posit that DODE could enhance the sensitivity of DDE-like experiments.

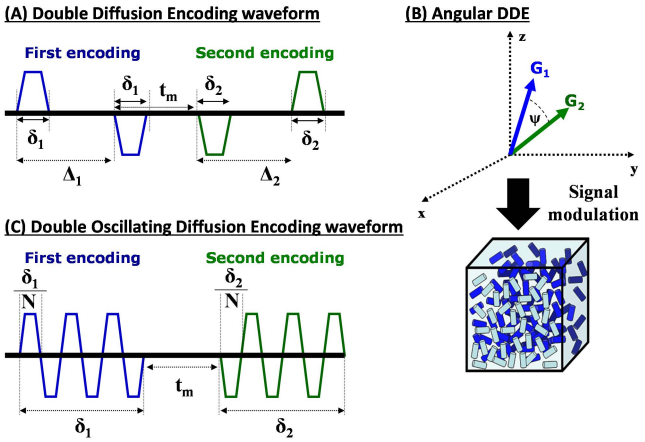

Figure 1. DDE and DODE sequences. **(A)** Conventional DDE sequence. **(B)** Angular DDE provides insights into μA in heterogeneous systems; **(C)** DODE sequences, comprising two oscillating gradient vectors having *N* oscillations each and separated by a mixing time.

Methods. All simulations were performed using the MISST framework [8-10] and carried out on a conventional laptop computer equipped with an Intel i5 processor and 8GB of RAM. Each curve was generated within less than 5 minutes. The model involved finite length, randomly oriented cylinders, with lengths of L=10 μm and radii of R=1 or 2 μm, and a diffusion coefficient of 1E-9 m^2/sec. Signals were confined to the intra-cylindrical space. DDE experiments are typically sought in the short diffusion gradient regime, and long diffusion separation regime [4]; our simulations were therefore carried out using $\delta_1=\delta_2=1$ms, $\Delta_1=\Delta_2=t_m=50$ms. The DODE sequence (Fig. 1C) was simulated with $\delta_1=\delta_2=50$ms and $t_m=50$ms (t_m is somewhat loosely defined in this sequence due to the multiple preceding gradient lobes), and the number of oscillations N was varied. For all simulations, $|\mathbf{G_1}|=|\mathbf{G_2}|=40$ G/cm.

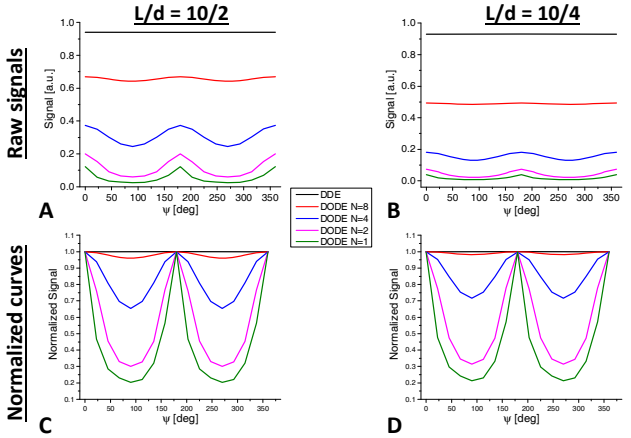

Figure 2. Simulations of DDE and DODE sequences via the MISST framework. **(A,B)** Raw signals for the two different scenarios analyzed. **(C,D)** Corresponding signals normalized to the ψ=0 point. Notice that the performance of the N=4, 8 sequences are most affected by the slightly modified μA.

Results and Discussion. Figure 2A shows simulations of DDE and of corresponding DODE experiments with varying numbers of oscillations for L/d = 10/2 and 10/4, respectively. Conventional DDE experiment–under these experimental conditions–will not convey the underlying compartment eccentricity for either system; indeed, Figures 2C and 2D, showing normalized signals, reveal that DDE's modulation is less than 1%. By contrast, DODE signals clearly convey the underlying microstructure via strong amplitude modulations. Very interestingly, the different scenarios seem to be contrast differently with N; for example, the N=4 sequence seems to be able to resolve the two scenarios, with $\psi(\pi/2)/\psi(0)$ = 0.72 and 0.64, respectively, while, the N=1 DODE sequence (which in fact is a DDE sequence with very long gradient durations), yields $\psi(\pi/2)/\psi(0)$ = ~0.2 for both scenarios. These results suggest a competition between signal attenuation due to accumulating diffusion weighting (e.g., increasing effective q-values), diffusion during gradient pulses (which, due to probing the boundaries whilst encoding diffusion, tend to reduce attenuation and thereby report on smaller apparent compartment sizes), and signal decay due to the parallel components of the signal (*n.b.* L/R>1). Much like SDE counterparts, such DDE sequences could be subject to optimization schemes [7] that would selectively probe subsets of randomly oriented cellular structures (e.g., neurites & astrocytic processes) classified by their microscopic anisotropy.

It is worth noting that DODE's signal enhancements can serve to (i) alleviate gradient-related constraints (including weak gradients and eddy currents); and (ii) provide better contrast to noise, allowing for reduced scanning time. Indeed, Finsterbusch [11] has proposed to successively concatenate multiple (short t_m) DDE blocks in the long diffusion time regime, and has shown that this affords significant signal enhancements. The DODE sequences shown herein could avoid prohibitively long echo times involved in concatenating numerous DDE sequences, or the use of signal-consuming stimulated echoes. Furthermore, we note that the MISST framework can be used not only to generate DODE signals, but also to fit DODE data, as the entire time sequence of gradients played out are taken into account. This provides a simple means of analyzing such experiments even prior to the generation of rigorous analytical expressions. Finally, implementing such sequences in clinical and preclinical scanners should not pose a great challenge, as most scanners can already perform oscillating gradient experiments (which are normally "paired", i.e., contain two gradient blocks); the only required modification is the manipulation of the second gradient's orientation (Fig. 1C); the enhancement of DDE's amplitude modulations offered by DODE sequences could indeed open up new possibilities for characterizing μA and underlying gray matter microstructures in clinical settings, where gradient amplitudes are generally limited to <6 G/cm.

Conclusions. DODE MR shows much potential for resolving micro-architectural features of the CNS, especially in the elusive gray matter.

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